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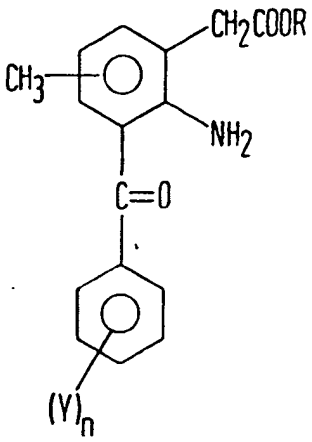
(71) Applicants
A H Robins Company Incorporated
1407 Cummings Drive
Richmond
Virginia 23220
United States of America
(72) Inventors
David Allan Walsh
Dwight Allen Shamblee
(74) Agents
Kilburn and Strode
30 John Street
London WC1N 2DD

(54) 2-amino-3-(halobenzoyl)-methylphenylacetic acids, esters and salts thereof

(57) Novel 2-amino-3-(halobenzoyl)-methylphenylacetic acids, esters and salts having the formula:



wherein R represents a hydrogen atom, a lower alkyl group or a pharmaceutically acceptable metal cation, Y represents a halogen atom and n is an integer from 1 to 3 are provided. The compounds exhibit outstanding anti-inflammatory and analgesic acitivity in warm blooded animals with minimal gastro-intestinal toxicity.

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SPECIFICATION

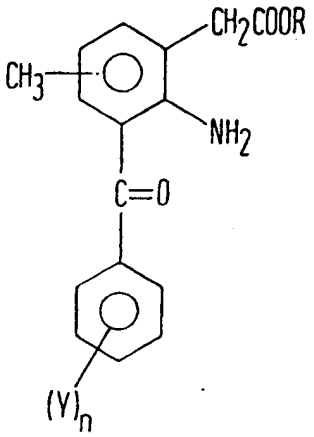
2-amino-3-(halob nz yl)-m thylph nylacetic acids, esters and salts th reof

The present invention relates to certain 2-amino-3-(halobenzoyl)-methylphenylacetic acids, their alkylesters and m tal salts, pharmaceutical compositions containing such compounds and pharmaceutical uses thereof.

Certain 2-amino-3-(5 and 6) benzoylphenylacetic acids having various substituents on the benzoyl and phenyl moieties and the methods of preparing and using the same are disclosed in U.S. Patent 4,045,576. The compounds of this reference are not methylphenylacetic acids or their derivatives.

U.S. Patent 4,221,761 discloses a process for the preparation of 7-acylindolin-2-ones which are intermediates in the preparation of the compounds of this invention.

The invention is more especially concerned with 2-amino-3-(halobenzoyl)methylphenylacetic acids, alkylesters and metal salts having the formula:



Formula I

wherein,

R. represents a hydrogen atom or a lower alkyl group or a pharmaceutically acceptable metal cation,

Y represents a halogen atom and

n is an integer from 1 to 3.

The novel compounds of this invention possess valuable pharmacological properties and are useful as pharmaceutical agents. The compounds exhibit outstanding anti-inflammatory and analgesic acitivity in warm blooded animals with minimal gasto-intestinal toxicity.

The present invention encompasses the compounds of Formula I set forth above with the accompanying definitions, pharmaceutical compositions comprising the compounds of Formula I and the compounds of Formula I for use in alleviating inflammation in living animals.

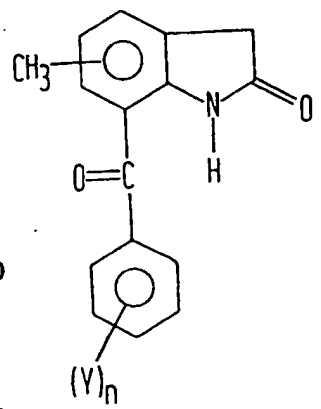
In the definition of symbols in the formulas hereof and where they appear elsewhere throughout this specification, the terms have the following meaning and significance.

The term "lower alkyl" as used herein includes straight and branched chain radicals of up to six carbon atoms inclusive, preferably no more than four carbon atoms and is exemplified by such groups as methyl, ethyl, propyl, isopropyl, butyl, secondary butyl, tertiary butyl, amyl, isoamyl and hexyl.

The term "halogen" when referred to herein includes chlorine, fluorine, bromine and iodine.

Illustrative of pharmaceutically acceptable metal cations are sodium, potassium, calcium, magnesium, zinc, aluminium, copper and hydrates thereof.

The compounds of this invention are conveniently prepared from a 7-benzoylmethylindolin-2-one of the formula:



wherein Y and n are defined above. These starting compounds may be prepared by conventional methods, such as those disclosed in U.S. Patents 4,045,576 and 4,221,716 mentioned above. The compounds of this invention are prepared by hydrolysis of the 7-benzoylmethylindolin-2-ones in aqueous basic solution to provide salts thereof which may then be acidified to obtain the acid. To obtain the lower alkyl esters thereof, the acid is converted to a metal salt which is then reacted in a suitable solvent with an alkyl halide to provide the desired ester.

The invention may be put into practice in various ways and a number of specific embodiments will be described to illustrate the invention with reference to the accompanying examples.

Example 1

Preparation of Sodium 2-Amino-3-(4-Fluorobenzoyl)-5-Methylphenylacetate Monohydrate.

A mixture of 8.0 grams (0.03 mol) of 7-(4-fluorobenzoyl)-5-methylindolin-2-one in 120 ml of 3N sodium hydroxide was heated at reflux for 16 hours. After diluting with water to 300 ml, the solution at a temperature of 50°C was titrated with concentrated hydrochloric acid to a pH of 8.2. The resulting orange solution was filtered and the filtrate obtained was cooled at 5°C and acidified to a pH of 4.5 with glacial acetic acid. The resulting yellow solid was collected and washed with water, then dissolved in methylene chloride. Water was added and the mixture was titrated with dilute sodium bicarbonate solution until a pH of 7.0 was maintained. The aqueous layer was separated and concentrated by boiling with absolute ethyl alcohol so as to remove water as the azeotrope. The yellow powder obtained was dissolved in isopropyl alcohol and one ml of water was added. After allowing the mixture to stand for 3 days, the resulting yellow solid was collected and dried at 25°C under high vacuum for 2 days to yield 1.6 grams (16.5% yield) of the title compound as a yellow powder having a m.p. of 140–160°C.

Analysis :	Calculated for $C_{16}H_{13}FNO_3Na.H_2O$	:	C,58.72;	H,4.62 N,4.28
	Found	:	C,58.71;	H,4.68 N,4.26

Example 2

Preparation of Sodium 2-Amino-3-(4-Chlorobenzoyl)-5-Methylphenylacetate.

Following the procedure of Example 1, a mixture of 11.5 grams (0.04 mol) of 7-(4-chlorobenzoyl)-5-methylindolin-2-one and 160 ml of 3N sodium hydroxide gave, after recrystallisation from water, 2.5 grams (18%) of the title compound as orange needles, m.p. 262°C.

Analysis :	Calculated for $C_{16}H_{13}ClNO_3Na$	:	C,59.00;	H,4.02; N,4.30
	Found		C,58.82;	H,4.09; N,4.32

Example 3

Preparation of sodium 2-Amino-3-(2,4-dichlorobenzoyl)-5-Methylphenylacetate.

Following the procedure of Example 1, a mixture of 7-(2,4-dichlorobenzoyl)-5-methylindolin-2-one and 3N sodium hydroxid produced the title compound.

Example 4

Preparation of Sodium 2-Amino-3-(2,3,5-Trichlorobenzoyl)-6-Methylphenylacetate.

Following the pr cedure of Exampl 1, a mixture of 7-(2,3,5-trichlorobenzoyl)-4-methylindolin-2-one and 3N sodium hydroxide produced the title compound.

Example 5

Preparation of Sodium 2-Amino-3-(4-Chlorobenzoyl)-4-M thylphenylacetate.

Following the procedure of Example 1, a mixture of 4-chlorobenzoyl-6-methylindolin-2-one and 3N sodium hydroxide produced the title compound.

Generally, in the past, strong anti-inflammatory drugs have been found to produce serious side eff cts of gastric bleeding and ulceration when administered orally to animals in effective amounts. The compounds of the present invention have been found to have the advantage that lowered incidence of gastric irritation is observed when they are administered in effective amounts for reducing inflammation as compared to indomethacin and the 2-amino-3-benzoyl-phenyl-acetic acids and their derivatives diclosed in U.S. Patent 4,045,576. For example, the compound of Example 2, sodium 2-amino-3-(4-chlorobenzoyl)-5-methylphenylacetate, was found to be approximately twice as potent as indomethacin and sodium 2-amino-3-benzoylphenylacetate but exhibited about 1/4 as much irritation to the stomach as indomethacin and about 1/2 as much irritation to the stomach as sodium 2-amino-3-benzoylphenylacetate. The compound of Example 2 was found to have about 1/2 the potency of sodium 2-amino-3-(4-chlorobenzoyl)-5-fluorophenylacetate but surprisingly exhibited about 1/4 as much irritation to the stomach as that compound.

The anti-inflammatory activity was demonstrated in laboratory animals using a modification of the Evans Blue-Carrageenan Pleural Effusion Assay of Sancilio, L. F., J. Pharmacol. Exp. Ther. *168*: 199-204 (1969).

Gastric toxicity was determined by a modification of the method of Tsukada et al., Arzneim. Forsch. *28*: 428–438 (1978).

The compounds of this invention also act as analgetics as determined by a modification of the method of Collier, et al., Brit. J. Pharmacol. Chemother. *32*: 295–310 (1968).

The present invention also contemplates novel compositions containing the compounds of the invention as active ingredients. Effective quantities of any of the foregoing pharmacologically active compounds may be administered to a living animal body in any one of various ways, for example, orally as in capsules or tablets, parenterally in the form of sterile solutions or suspensions, and in some cases intravenously in the form of sterile solutions. In forming the novel compositions of this invention, the active ingredient is incorporated in a suitable carrier, illustratively, a pharmaceutical carrier. Suitable pharmaceutical carriers which are useful in formulating the compositions of this invention include starch, gelatin, glucose, magnesium carbonate, lactose and malt. Liquid compositions are also within the purview of this invention and suitable liquid pharmaceutical carriers include ethyl alcohol, propylene glycol, glycerine and glucose syrup.

The pharmacologically active compounds may be advantageously employed in a unit dosage of from 0.1 to 150 milligrams. The unit dosage may be administered once daily or in multiple or divided daily doses. The daily dosage may vary from 0.3 to 450 milligrams. Five to 25 milligrams appears optimum per unit dose.

It is only necessary that the active ingredient constitute an effective amount i.e., such that a suitable effective dosage will be obtained consistent with the dosage form employed. The exact individual dosages as well as daily dosages will, of course, be determined according to standard medical principles under the direction of a physician or veterinarian.

The active agents of the invention may be combined with other pharmacologically active agents, or with buffers, antacids or the like, for administration and the proportion of the active agent in the composition may be varied widely.

The following are examples of compositions formed in accordance with this invention.

Examples 6A to 6C

Capsules of 5 mg (Example 6A), 25 mg (Example 6B) and 50 mg (Example 6C) of active ingredient per capsule were prepared. With the higher amounts of active ingredient, adjustment may be made in the amount of lactose.

Example 6A

Typical blend for encapsulation	Per capsul , mg
Active ingredient	5.0
Lactose	296.7
Starch	129.0
Magn sium st arate	4.3
Total	435.0 mg

Additional capsule formulations preferably contain a higher dosage of active ingredient and are as follows:

Example 6B

Ingredients	Per capsule mg
Active ingredient	25.0
Lactose	306.5
Starch	99.2
Magnesium stearate	4.3
Total	435.0 mg

In each case the selected active ingredient was uniformly blended with lactose, starch, and magnesium stearate and the blend then encapsulated.

Example 7

A typical formulation for a tablet containing 5.0 mg of active ingredient per tablet follows. The formulation may be used for other strengths of active ingredient by adjustment of the weight of dicalcium phosphate.

		Per tablet, mg
(1)	Active ingredient	5.0
(2)	Corn starch	13.6
(3)	Corn starch (paste)	3.4
(4)	Lactose	79.2
(5)	Dicalcium phosphate	68.0
(6)	Calcium stearate	0.9
		170.1 mg

Ingredients 1, 2, 4 and 5 were uniformly blended. Ingredient 3 was prepared as a 10 per cent paste in water. The blend was granulated with starch paste and the wet mass passed through an eight mesh (US sieve) screen (which has openings of 2.38 mms). The wet granulation was dried and sized through a twelve mesh (US sieve) screen (which has openings of 1.68 mms). The dried granules were blended with calcium stearate and pressed.

Example 8

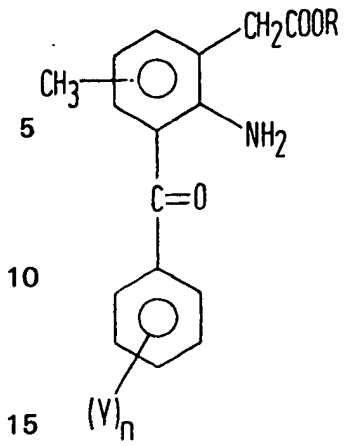
Injectable – 2% sterile solutions may be made as follows:

	Per cc
Active ingredient	20 mg
Preservative, e.g. cholorobutanol	0.5% weight/volume
Water for injection	q.s.

The solution was prepared, clarified by filtration and filled into vials which were then sealed and autoclaved.

CLAIMS

1. A compound having the formula:



wherein;

R represents a hydrogen atom, or a lower alkyl group or a pharmaceutically acceptable cation,

Y represents a halogen atom, and

n is an integer from 1 to 3.

2. 2-Amino-3-(4-fluorobenzoyl)-5-methylphenylacetic acid.

3. Sodium 2-amino-3-(4-fluorobenzoyl)-5-methyl-phenylacetate monohydrate.

4. 2-Amino-3-(4-chlorobenzoyl)-5-methylphenylacetic acid.

5. Sodium 2-amino-3-(4-chlorobenzoyl)-5-methyl-phenylacetate.

6. A compound as claimed in Claim 1 substantially as specifically described herein with reference to any one of Examples 1 to 5.

7. A pharmaceutical composition suitable for alleviating inflammation and pain in a living animal body comprising an effective amount of a compound as claimed in any one of Claims 1 to 6 and a pharmaceutically acceptable carrier or diluent thereof.

8. A composition as claimed in Claim 7 substantially as specifically described herein with reference to any one of Examples 6A to 8.

9. A compound as claimed in any one of Claims 1 to 6 or a composition as claimed in Claim 7 or Claim 8 for use in alleviating inflammation in a living animal body.

10. A compound as claimed in any one of Claims 1 to 6 or a composition as claimed in Claim 7 or Claim 8 for use in alleviating pain in a living animal body,

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